UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,470	01/07/2005	Thomas Tuschl	2923-673	5503

6449 7590 12/11/2007

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
12/11/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/520,470	TUSCHL ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2007 and 19 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9,11-16,20,22-36 and 38-41* is/are pending in the application.

4a) Of the above claim(s) *22-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9,11-16,20,32-36 and 38-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on and October 29, 2007.

Currently, claims 1, 3-9, 11-16, 20, 32-36, and 38-41 are under examination on the merits in the instant case.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 40 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 40 recites the limitation "The pharmaceutical composition according to claim 20" in line 1. There is insufficient antecedent basis for this limitation in the claim, because as currently amended, claim 20 does no longer recite "A pharmaceutical composition"; it now recites, "A composition".

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 40 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not

be undue experimentation. The key word is 'undue', not 'experimentation'." (Wands, 8 USPQ2d 1404). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claim is directed to a pharmaceutical composition comprising a single-stranded RNA molecule that inhibits target gene expression by RNA interference. As such, the claimed invention must confer therapeutic effects when administered to a subject *in vivo*.

As extensively discussed in the previous Office action dated June 27, 2007, the instant specification provides only *in vitro* examples wherein a single-stranded RNA inhibits target transcript expression in human HeLa cell extracts and is silent about *in vivo* working examples. It was also discussed that the state of the prior art, the level of one of ordinary skill, and the level of predictability in the art of RNAi-mediated gene therapy were considered nascent at the time of the invention. See pages 5-7 of the previous Office action. In view of the totality of the factors and reasons stated above and in the previous Office action, one of ordinary skill in the art would not have made and used the claimed pharmaceutical composition solely based on the *in vitro* examples disclosed in the instant application. Since reduced expression of target transcripts in HeLa cells is not indicative of pharmaceutical effects or representative of pharmaceutically related compositions, and since there is neither positive *in vitro – in vivo* correlation nor

sufficient *in vivo* data, and since the general teachings in the art are such that nucleic acid-based therapeutics or *in vivo* use remain unpredictable, one of ordinary skill in the art would not have made and used the instantly claimed pharmaceutical composition with a resultant therapeutic effect at the time the invention was made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-9, 11-16, 20, 32-36, 38-39, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tijsterman et al. (citation or record) in view of Elbashir et al. (*Nature,* 2001, 411:494-498) and McSwiggen (US 2003/0153521 A1).

In the instant case, the independent claim, claim 1, has been currently amended. Hence, by virtue of claim dependency, all dependent claims are currently amended as well.

The claims are drawn to a method of inhibiting a target transcript expression in human cells *in vitro,* comprising introducing a single-stranded RNA molecule that mediates RNA interference, wherein the molecule is 14-50 nucleotides in length, and at least 20 nucleotides at the 5' region are fully complementary to said target transcript, wherein the RNA molecule comprises at least one chemically modified sugar backbone or ribonucloetide.

Tijsterman et al. teach a method for inhibiting the transcript of target gene GFP comprising contacting a single-stranded RNA molecule that is 25 nucleotides in length (page 695). They also teach a method of triggering RNAi with unc-22 antisense single-stranded RNAs (page 695). They teach that *in vivo* siRNAs are predominantly expressed as antisense RNAs and that first step of RNAi is bypassed by single-stranded antisense administration (pages 695-696). Furthermore, they teach that single-stranded antisense RNAs of at least 22 nucleotides and up to 40 nucleotides in length are capable of forming dsRNAs that become substrates for DICER-dependent degradation, therefore via RNAi (page 696). Tijsterman et al. do not teach that the method is performed in human cells *in vitro*, nor do they teach chemical modifications.

Elbashir et al. teach a method of inhibiting target transcript expression in mammalian cells *in vitro* by RNA interference, wherein the mammalian cells include cultured human cells. They teach that RNAi interference in human cell culture provides great analytical and investigational tools to study gene-specific therapeutics and gene function. See the entire reference.

McSwiggen teaches that RNAi-inducing RNA molecules can be chemically modified for increased stability. He also teaches that a 5'-phosphate moiety on the antisense strand of the RNAi-inducing RNA molecule is required for RNAi activity in cells (paragraphs 0112, 0139-0141, 0145, 0154-0155, 0159; claims 1-7, 19).

It would have been obvious to one of ordinary skill in the art to modify the single-stranded RNAi molecule of Tijsterman et al. to include stabilizing chemical modifications of McSwiggen et al. and apply the chemically modified RNAi molecule to inhibit human genes in cultured human cells *in vitro* as taught by Elbashir et al.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success because the use of a single-stranded RNA molecule to inhibit target gene transcript expression by RNA interference was known in the art as taught by Tijsterman et al., and because incorporating chemical modifications such as the claimed 5'-phosphate moiety, phosphoramidate, and ethoxymethyl were known to increase stability of the RNAi-inducing molecules as taught by McSwiggen, and because RNA interference performed in cultured human cells was known to be useful for investigating gene-specific therapeutics or gene functional diagnostics as taught by Elbashir et al. Since both skills and knowledge necessary to arrive at the claimed invention were within the technical grasp of one of ordinary skill in the art at the time of the invention, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

This application contains claims 22-31 drawn to inventions nonelected without traverse in the reply filed on June 4, 2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
Primary Examiner
Art Unit 1635